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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,678	MONTE ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9,14-16,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9, 14-16, 35, 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 7-9, 14-16 and 35-36 are pending examination.

The amendment to the specification (cross reference), amendment to claims 7, 8, 15, and the addition of new claims 35-36 and applicants' traversal in paper no. 13 is acknowledged and considered.

The objection to claims 7, 8, and 15 is moot in view of the amendment to the claims. See page 6 of paper no. 13.

Information Disclosure Statement

After further consideration articles AR-AT will be placed in the file and not be initialed because they are not published documents.

Claim Objections

Claim 7 is objected to for reciting grammatically improper phase, "all of whose germ and somatic cell line." Amending the claims to recite 'whose germ and somatic cells," would obviate this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9, 14, 16, and 35-36, as best understood, are readable on a genus of a transgenic non-human animal comprising a nucleotide sequence comprising at least 90% homology to SEQ ID NO: 1, wherein the genus of the transgenic animals are not claimed so that

they could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of transgenic animals comprising a nucleotide sequence set forth in SEQ ID NO: 1 or a sequence, which is at least 90% homologous thereto, wherein said DNA molecule is expressed in one or more cells of said animal, and wherein said DNA codes for a protein that has an activity of Ad7c-NTO when **expressed** in neuronal cells. The starting material for making a transgenic animal is a nucleotide sequence set forth in SEQ ID NO: 1 or a sequence with at least 90% homology thereto. The specification provides sufficient description of a species of expression of AD7c-NTP, which induces neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a human when **over-expressed**. However, the as-filed specification does not provide an adequate written description of a representative number of species of nucleotides sequences comprising a DNA molecule with at least 90% homology with SEQ ID NO: 1, wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when **expressed** in neuronal cells. It is apparent from the state of the prior art exemplified by Ngo *et al.* (The Protein Folding Problem and Tertiary Structure Prediction, Birkhauser Boston, 1994, pp. 491-494) and Chiu *et al.* that the description of the primary sequence of amino acid residues in which the positions of the amino acid residues are particularly arranged is essential for the biological function of the protein encoded by the sequence when over-expressed in neuronal cells. This essential element (starting material) that is required for an adequate description of a representative number of species as

embraced by the claimed genus of a DNA molecule with at least 90% homology to SEQ ID NO: 1 is neither described sufficiently in the specification nor conventional in the prior art. A mere statement asserting that any sequence having at least 90% homology to SEQ ID NO: 1 without providing the essential and specific arrangement of the amino acid residues positioned in the sequence does not lend evidentiary support for a skilled artisan to have recognized that applicant was in possession of the genus of DNA molecules with at least 90% homology to SEQ ID NO: 1 as claimed, particularly since the essential element of the coding of a protein or variant thereof other than SEQ ID NO. 1 that is yet be discovered, is lacking from the as-filed specification and since the skill and knowledge in the art is not adequate or conventional to determine the primary sequence of the representative number of species of SEQ ID NO: 1 (e.g. allelic variants, orthologs, 90% homology to SEQ ID NO: 1, etc.) that has an activity of AD7c-NTP when expressed in neuronal cells on the basis of the disclosure of only SEQ ID NO: 1. Thus, the as-filed specification only provides sufficient description of a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is 90% homologous thereto, wherein said DNA molecule is **over-expressed** in neuronal cells that results in neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites.

The specification contemplates a genus of transgenic animals comprising a nucleotide sequence set forth in SEQ ID NO: 1 or a sequence, which is at least 90% homologous thereto. The starting material for making a transgenic animal is a nucleotide sequence set forth in SEQ ID NO: 1 or a sequence with at least 90% homology thereto. The specification provides sufficient description of SEQ ID NO: 1 and a specific functional limitation (neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a

human when **over-expressed**), however, the specification does not provide sufficient description of any transgenic animal comprising a sequence with at least 90% homology to SEQ ID NO: 1 and its corresponding phenotype (neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a non-human animal when **expressed**). Therefore, in view of the lack of sufficient description of the corresponding phenotype, one skilled in the art could not envision the phenotype of any transgenic animal comprising a sequence with at least 90% homology to SEQ ID NO: 1 that has an activity of AD7c-NTP when expressed in neuronal cells. Thus, the as-filed specification only provides sufficient description of a transgenic non-human animal whose genome comprises a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is 90% homologous thereto, wherein said DNA molecule is **over-expressed** in neuronal cells that results in neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites.

Furthermore, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of transgenic animals comprising a nucleotide sequence set forth in SEQ ID NO: 1 or a sequence with 90% homology thereto as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of nucleotide sequences with 90% homology to SEQ ID NO: 1 that must exhibit the disclosed biological functions as contemplated by the claims (**over-expressed** in neuronal cells that results in neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites).

It is not sufficient to support the present claimed invention directed to a genus of transgenic animals comprising a nucleotide sequence which is at least 90% homology to SEQ ID NO: 1 and any corresponding phenotype other than the phenotype set forth above when said molecule is over-expressed in neuronal cells. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming unspecified transgenic non-human animals comprising a nucleotide sequence with at least 90% homology to the nucleotide sequence set forth in SEQ ID NO: 1 that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of transgenic non-human animals comprising a nucleotide sequence which is at least 90% homology to SEQ ID NO: 1 or any other phenotype than the one set forth above that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was

made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicants traverse the rejection under 112 written description for the following reasons: the proposition that a genus of DNA molecules that are at least 90% homologous to a disclosed nucleotide sequence is supported by Example 14 of the written description synopsis, which encompasses a protein having SEQ ID NO: 3 and variants thereof that are at least **95%** identical to SEQ ID NO: 3 with a specific functional limitation; according to Example 14 procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art, likewise for making DNA molecules which are at least 90% homologous to SEQ ID NO: 1; it is not necessary for a skilled artisan to be able to envision any particular phenotype that the claimed transgenic animals may or may not possess. See pages 7-14.

Applicants' traversal is acknowledged and is not found partially persuasive for the following reasons: the as-filed specification provides sufficient description for a genus of a transgenic non-human animal whose genome comprises a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is 90% homologous thereto, wherein said DNA molecule is **over-expressed** in neuronal cells that results in neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites.

However, applicants' traversal is not found persuasive the for a genus of a transgenic non-human animal comprising a nucleotide sequence comprising at least 90% homology to SEQ ID NO: 1 for the reasons set forth above. More specifically, the as-filed specification does not provide sufficient description of a representative number of species of transgenic non-human

animals whose genome comprises a DNA molecule which is 90% homologous to SEQ ID NO: 1 and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when expressed in neuronal cells. The as-filed specification and the applicants' traversal fail to provide essential nucleotides or amino acid residues for a representative number of sequences, wherein each sequence is composed of at least 90% homology to SEQ ID NO: 1 that an activity of AD7c-NTP when expressed (under expressed, normal expression) in neuronal cells.

Furthermore, the as-filed specification does not provide sufficient description of a phenotype of a transgenic animal comprising a nucleotide sequence that is 90% homologous to SEQ ID NO: 1 if a phenotype comprising neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in neuronal cells in neuronal cells is not observed in the transgenic animal. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Thus, the claims are claiming subject matter that is not supported by the disclosure.

Claims 7-9, 14-16 remain and claims 35-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a transgenic animal comprising a nucleotide sequence comprising a DNA molecule which is at least 90% homologous to SEQ ID NO: 1 and its corresponding phenotype when the protein is expressed in neuronal cells), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. for use in a method for testing potential Alzheimer's Disease drugs.

Furthermore, with respect to the claimed invention, which is directed to the starting material set forth in SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous thereto for use in a method for producing a transgenic non-human animal, which over-expresses SEQ ID NO: 1, the as-filed specification does not provide sufficient guidance for one skilled in the art to make and/or use any DNA molecule which is at least 90% homologous to SEQ ID NO: 1. The as-filed specification provides sufficient guidance of a nucleic acid sequence set forth in SEQ ID NO: 1. However, the as-filed specification does not provide sufficient guidance for how one skilled in the art would be enabled to reasonably correlate SEQ ID NO: 1 to a nucleic acid which is at least 90% homologous to SEQ ID NO: 1, since at the time the application was filed, predicting any protein tertiary structure based on a protein structure was considered to be unpredictable due to significant problems in several areas. The state of the art in 1998, exemplified by Chiu et al., *Folding and Design*, Vol. 3, pg. 223-228, May 1998, Chiu displays major consideration for predicting a protein tertiary structure involve issues that include:

> Predicting the three-dimensional conformation of a correctly folded protein can be divided into two distinct steps: the construction of a fitness function to evaluate the various conformations: and the search through various possible conformations for the "best" prediction most likely to represent the native state. Neither part of this problem

> has proven particularly tractable. The development of a general method for the prediction of protein tertiary structure based on the protein sequence remains, unfortunately, one of the great-unsolved problems of computational biophysics (pg. 223).

Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of a transgenic animal comprising a nucleotide sequence with 90% homology to SEQ ID NO: 1 as recited in the claims, particularly in view of the reasons set forth above and the breadth of the claims, one skilled in the art would not have known how to make and/or use the claimed invention so that it would operate as intended, *e.g.* a nucleic acid sequence with at least 90% identity to SEQ ID NO: 1 protein for use in a method of producing a transgenic animal that over-expresses SEQ ID NO: 1 or a nucleic acid sequence with at least 90% identity to SEQ ID NO: 1. This unpredictability of the relationship between sequences and function, albeit that certain specific sequences may be found to be conserved over sequences of related function upon a significant amount of further research. Since there are numerous nucleotide sequences with 90% homology to SEQ ID NO: 1 and the art of record displays nucleotide sequences with at least 90% homology to SEQ ID NO: 1 and they each possess a different function and that one skilled in the art would understand that altering amino acids in a sequence can change or destroy the desired function of the sequence, it would take one skilled in the art an undue amount of experimentation to reasonably determine what sequences with at least 90% homology to SEQ ID NO: 1 possess the desired function. Therefore, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from SEQ ID NO. 1 to any sequence that has at least 90% homology to SEQ ID NO: 1 because of the unpredictability provided by the art of record.

Furthermore, even if the applicants are able to overcome the concerns for 112 written description and enablement issues for a DNA molecule which is at least 90% homologous to SEQ ID NO: 1, there are still concerns with state of the art for producing transgenic animals with a desired phenotype since the art is considered unpredictable. The specification discusses that the invention features a genus of transgenic non-human animals, which over-expresses SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous thereto and goes on to contemplate that there are techniques available for producing transgenic animals (page 20). The specification provides prior art pertaining to methods for generating transgenic mammals using fertilized eggs and pro-nuclei injection (page 20). The specification requires that the starting material, which is a nucleic acid set forth in SEQ ID NO. 1 or a DNA molecule which is at least 90% homologous thereto, be used in a method of making a transgenic non-human animal comprising over-expressing SEQ ID NO: 1 or a sequence with 90% homology thereto. The specification contemplates that the transgenic animals can be used in a method for identifying compounds that could be potential useful for the treatment or prevention of Alzheimer's disease (AD) (page 21). In addition, the specification states that SEQ ID NO: 1 is observed in patients with (AD). However, the as-filed specification does not provide sufficient guidance or factual evidence for any transgenic animal expressing a nucleotide sequence encoding SEQ ID NO: 1 or a DNA molecule, which is at least 90% homologous thereto, and any corresponding phenotype.

It is further to note that the as-filed specification only contemplates the use of embryonic stem (ES) cell technology or using pro-nuclear injection for the generation of transgenic mammals for used in the claimed invention. See page 20 of the specification. The state of the art at the time application was filed for producing transgenic animals using pro-nuclear injection

was considered unpredictable as exemplified by Polejaeva et al. Theriogenology, Vol. 53, pages 117-126, 2000, Polejaeva states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke et al. disclose, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Reprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

> The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic non-human animal comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for

use in the production of any transgenic mammal, the state of the art supports that only mouse ES cells were enabled for used in the production of transgenic mice. In view of the concerns set forth by the state of the art, the examples do not reasonably address the concerns put forth by the state of the art encompassing any method for producing transgenic mammals for use in over-expressing SEQ ID NO: 1 or a sequence with 90% homology to SEQ ID NO: 1. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification and the prior art to any transgenic animal over-expressing SEQ ID NO: 1 or a sequence with 90% homology thereto. In addition, in view of the concerns stated above encompassing microinjection and random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a DNA sequence set forth in SEQ ID NO: 1 is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any transgenic non-human animal. Furthermore, each animal comprises of a distinct genome and the specification does not provide sufficient guidance for how to avoid random integration of a DNA molecule set forth in SEQ ID NO: 1, which would result in the characteristics set forth in the specification. In addition, Trojanowski teaches that certain characteristic can be produce in a test tube, the conditions required are highly artificial and in vitro paradigms have limited utility as models of in vivo mechanisms of neurodegeneration (Brain Pathology, Vol. 9, page 737, 1999). Thus, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from a human having AD that endogenously over-expresses AD7c-NTP to a transgenic animal expressing AD7c-NTP with a desired phenotype because of the art of record and the distinct genomic structure of each animal.

In addition, the disclosure fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic animals comprising a transgenic sequence encoding SEQ ID NO: 1 or a sequence with 90% homology thereto, which expresses the transgenic sequence such that a phenotype occurs. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any contemplated transgenic animal of the invention when the nucleotide sequence is expressed and not over-expressed in said animal. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic mammal over-expressing SEQ ID NO: 1 or a sequence with 90% homology thereto.

[Note that although the claimed transgenic mammal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic mammal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mammal would serve if the transgene (e.g. SEQ ID NO: 1 or a sequence with 90% homology thereto) is not expressed at a sufficient level for a resulting phenotype).]

As the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human mammals as

claimed, one skilled in the art would not be able to rely on the state of the art for an attempt to produce any transgenic animals. This is because of the art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animal comprising a transgene of interest (e.g. SEQ ID NO: 1 or a sequence with 90% homology thereto); it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For example, the level and specificity of expression of a transgene (e.g. SEQ ID NO: 1 or a sequence with 90% homology thereto) as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified animals, which exhibit a particular phenotype. This observation is supported by Wall (Theriogenology, 1996) who states "Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc. The specification does not provide sufficient guidance, and it fails to feature any reasonable correlation between producing transgenic animal using microinjection of transgene into germ line and producing a transgenic animal which comprises a transgenic

sequence encoding SEQ ID NO: 1 or a sequence with 90% homology thereto and which over-expresses the protein in the transgenic mammal, and, thus, a specific resulting phenotype.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report "transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies." See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 239-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic animal that over-expresses SEQ ID NO: 1 or a sequence with 90% homology thereto, it would require an undue amount of experimentation to reasonably predict the results achieved in any transgenic mammal comprising a transgenic sequence set forth in SEQ ID NO: 1 or a sequence with 90% homology thereto and which over-expresses the protein in the transgenic animal at the levels of the claimed product, the consequences of that production, and therefore, the resulting phenotype.

Furthermore, even if the applicants are able to overcome the enablement rejection for producing a transgenic animal, the following rejection under enablement with respect to claim

14-16 follows. Claims 14-16, which encompass an in vivo method for screening a candidate drug that is potentially useful for treatment or prevention of Alzheimer's Disease, neuroectodermal tumors, malignant astrocytomas, and glioblastomas, the as-filed specification only provides sufficient guidance for one skilled in the art to use the method for screening for drugs that could reduce one of the diseases described above. The as-filed specification provides sufficient guidance for the symptoms of these diseases after the diseases have been observed, however, the as-filed specification does not provide sufficient guidance for how to use the method for identifying drugs that can be used to treat or prevent any of the diseases set forth above. The art of record teaches that there is no animal model that can mimic all the cognitive, behavorial. Biochemical, and histopathological abnormalities observed in a patient with AD (Yamada et al., Pharmacology & Therapeutic, Vol. 88, 93-113, 2000). Furthermore, the art of record is absent about a drug that is able to treat or prevent any of these diseases listed above and teaches that it should be possible to discover novel drugs that slow the progress or alleviate the clinical symptoms of AD by using animal models. Therefore, in view of the lack of guidance and/or factual evidence for any drug that can be used to treat or prevent any of the claimed diseases, it would take one skilled in the art an undue amount of experimentation to use the claimed method for identifying a drug that could treat or prevent Alzheimer's Disease, neuroectodermal tumors, malignant astrocytomas, and glioblastomas.

Thus, in view of the In re Wands' Factors, the disclosure is not enabled for claimed invention because in view of the undue quantity of experimentation necessary to determine the parameters listed above for the starting material, the lack of direction and/or sufficient guidance provided by the as-filed specification for the production of any transgenic non-human animal

with a particular phenotype when a nucleotide with 90% homology to SEQ ID NO: 1 is expressed in said animal. Furthermore, the lack of working examples for the demonstration or the reasonable correlation to the production of any transgenic animal, in particular when the expression of the SEQ ID NO: 1 must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human animals of any species, and the breadth of the claims drawn to any transgenic non-human animal, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants traverse the rejection under 112 enablement for the following reasons in view of the three distinct bases that the Examiner has set forth in support of the rejection of lack of enablement:

1) Applicants' traverse the rejection under enablement because of the lack of a written description for the subject matter encompassed by Applicants' claims because the claims are supported by the specification. See pages 15-16.

The applicants' traversal for the rejection set forth above is acknowledged and is found partially persuasive for the following reason set forth under the response to applicants' traversal for written description. However, the traversal is not found persuasive for the claimed invention for the reasons set forth above under enablement.

2) Applicants' traverse the rejection under enablement for making and using a nucleotide sequence with 90% homology to SEQ ID NO: 1 for the following reasons: A person of ordinary skill in the art would be able to make a DNA molecule that are at least 90% homologous to SEQ ID NO: 1 and test them for the ability to encode proteins that possess AD7c-NTP activity; any

uncertainty that is associated with predicting protein function from sequence data is of little relevance in an analysis of the enablement of applicants' claims; It is possible that there are DNA molecules that are at least 90% homologous to SEQ ID NO: 1 but that do not encode proteins with AD7c-NTp activity may be identified by the methods set forth in the as-filed specification. See pages 16-20.

The applicants' traversal is not found persuasive for the claims for the reasons set forth above. More specifically, the as-filed specification only provides sufficient guidance for SEQ ID NO: 1 when the sequence is over-expressed in *in vitro* neuronal cells. However, the as-filed specification does not provide sufficient guidance for a representative number of species of transgenic animals comprising a nucleotide sequence that has an activity of AD7c-NTP when expressed in neuronal cells. Thus, it would take one skilled in the art an undue amount of experimentation for one skilled in the art to reasonably extrapolate from SEQ ID NO: 1 and its biological function when over-expressed in isolated neuronal cells to any sequence with 90% homology to SEQ ID NO: 1 that has activity of AD7c-NTP when expressed in neuronal cells because the specification does not provide sufficient guidance for the full scope of AD7c-NTP activities when it is normally expressed or under-expressed in neuronal cells. Furthermore, the as-filed specification or the applicants' traversal lacks sufficient or factual evidence for which specific sequences exhibit the function as contemplated by the breadth of the claims (same activity as AD7c-NTP when over-expressed in neuronal cells) since it is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the nucleotide sequence in many instances. The effects of these changes are largely unpredictable as to which mutation has a significant effect versus not (see

Chiu and Ngo). It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, with respect to the assertion that the specification provides methods for obtaining DNA molecule, which are at least 90% homologous to SEQ, ID NO: 1 that has AD7c-NTP activity when **expressed** in neuronal cells.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification and the applicants' traversal (See page 18 of traversal, which states, "the specification provides various methods for assaying for AD7c-NTP activity" and "it is possible that DNA molecules that are at least 90% homologous to SEQ ID NO: 1 but that do not encode proteins with AD7c-NTp activity may be identified by the methods described above") provide no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using any nucleotide sequence with 90% homology to SEQ ID NO: 1 that has an activity of AD7c-NTP when **expressed** in neuronal cells, for those skilled in the art to experiment with level of expression so as to provide a nucleotide sequence with the same activity of SEQ ID NO: 1 (overexpression of SEQ ID NO: 1 in neuronal

cells results in the reduction of frequency of at least one neuritic sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons in the host) or an activity that is not supported by the disclosure. As intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what amino acids are required for a DNA molecule codes for a protein that has an activity of AD7c-NTP when **expressed** in neuronal cells, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the assertion in the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the claimed invention. Thus, the assertion that assays are routine for one skilled in the art results in an unpredictable and therefore unreliable correspondence between the sequences and the biological activity of known function and therefore lacks support regarding enablement.

3) Applicants' traverse the rejection under enablement for producing a transgenic non-human animal whose genome comprises SEQ ID NO: 1 or a nucleotide sequence with 90% homology to SEQ ID NO: 1 for the following reasons: It is incorrect to state that the specification only contemplates the use of ES cell technology and pro-nuclear injection to produce non-human

transgenic animals; The examiner has not provided evidence that would indicate that transgenic animal production using pro-nuclear microinjection or embryonic stem cell technology would entail a degree of experimentation that would be regarded as undue in the context of the present invention; Any method known to one skilled in the art can be used for the production of the transgenic animals of the invention; transgenic animals of the present invention even if they do not exhibit a particular phenotype would nonetheless be useful in drug screening in the treatment or prevention Alzheimer's Disease, Phenotypes are described in the specification (see page 20). See pages 21-32.

The applicants' traversal is not found persuasive for the claimed invention for the reasons set forth above under enablement. More specifically, the as-filed specification does not provide sufficient guidance for a transgenic non-human animal whose genome comprises a nucleotide sequence set forth in SEQ ID NO: 1 with the characteristics cited in the specification when the sequence is expressed in neuronal cells. Furthermore, the as-filed specification does not provide sufficient guidance for a representative number of species of transgenic animals whose genome comprises a nucleotide sequence that has an activity of AD7c-NTP when expressed (under expression, normal expression, over-expressed) in neuronal cells. Thus, in view of the art of record (e.g. Trojanowski) for extrapolating from in vitro results to an in vivo phenotype, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from no working example and an *in vitro* culture comprising SEQ ID NO: 1 and its biological function when over-expressed to any transgenic animal whose genome comprises a sequence set forth in SEQ ID NO: 1 or a sequence with 90% homology to SEQ ID NO: 1 that has activity of AD7c-NTP when expressed in neuronal cells of said animal because the specification does not provide

sufficient guidance for the scope of AD7c-NTP activities when it is normally expressed or under-expressed in neuronal cells in vivo.

It is acknowledged that there are several methods to produce transgenic animals that are known in the art, however, the art of record provides concerns associated with predicted a desired phenotype in a transgenic animal (e.g. Trojanowski, Rulicke, Mullins, Polejaeva). However, the rejection is directed to the unpredictability and the lack of working examples for the demonstration and/or the reasonable correlation to the production and using of any transgenic animal, in particular when the expression of the AD7c-NTP must occur at a level resulting in a **corresponding phenotype.** However, in view of the art of record displaying the unpredictability of random integration of DNA into a cell's genome and transgene behavior, and the lack of guidance provided by the traversal and/or the specification for making and using transgenic non-human animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mammal would serve if the transgene (e.g. AD7c-NTP) is not expressed at a sufficient level for a resulting phenotype).

Furthermore, it is not apparent to one skilled in the art how to perform an assay for screening a candidate drug of Alzheimer's disease, neuroectodermal tumors, malignant astrocyomas, and glioblastomas in a transgenic animal comprising a nucleotide sequence that is 90% homologous to SEQ ID NO: 1 if a phenotype comprising neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in neuronal cells is not observed in the transgenic animal. Thus, the as-filed specification is claiming subject matter that is not supported by the disclosure.

Furthermore, with respect to the assertion that the specification provides methods for obtaining a genus of transgenic non-human animals comprising a stably integrated DNA molecule, which are at least 90% homologous to SEQ ID NO: 1 that has AD7c-NTP activity when **expressed** in neuronal cells.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification and the applicants' traversal (See page 27 of traversal, which states, "transgenic animals of the present invention, even if they do not exhibit a particular phenotype, would nonetheless by useful for drug screening applications" provide no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using any transgenic non-human animal comprising a nucleotide sequence with 90% homology to SEQ ID NO: 1 that has an activity of AD7c-NTP when expressed in neuronal cells, for those skilled in the art to experiment with level of expression so as to provide any other characteristic not supported by the specification other than the characteristics observed in neuronal cells of an AD patient or in vitro neuronal cells that results in the reduction of frequency of at least one neuritic sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons in the host) as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what amino acids are required for a DNA molecule codes for a protein that has an activity of AD7c-NTP when **expressed** in neuronal cells for use in producing a transgenic non-human animal with a phenotype not supported by the as-filed specification, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the assertion in the specification to the claimed invention. Therefore, the as-filed specification is not enabled for the full breadth of the claimed invention.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
10/21/02

DAVET NGUYEN
PRIMARY EXAMINER